general practitioners in Tameside to vaccinate patients at all stages of HIV disease.

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. . . though vaccine's efficacy is unproved

EDITOR,—A Jain and colleagues elegantly reviewed published work on the efficacy of pneumococcal vaccine in HIV infection.[1] Failure of protection in the United Kingdom has been reported and the question of efficacy raised elsewhere.[2,3] We recently conducted a postal survey of 176 consultants in genitourinary medicine in the United Kingdom on the routine vaccination of HIV positive patients with pneumococcal vaccine. Preliminary data show that only 25 of the 129 consultants who replied offer the vaccine as part of their clinic policy. Only one of the 28 consultants who replied from the London boroughs offers the vaccine routinely, which is similar to the figure obtained by Jain and colleagues.

We think that the Joint Committee on Vaccination and Immunisation of the departments of health of the United Kingdom may have been a little premature in recommending the routine use of pneumococcal vaccine in all HIV positive patients without considering the evidence for clinical efficacy in this group of patients. Some people think that vaccinations may have a deleterious effect on the progression of HIV disease, whereas others have suggested using a double dose, as advocated for other vaccines. Interestingly, most of the consultants caring for HIV positive patients in this country do not follow the recommendations. There could be medicolegal implications if an unvaccinated HIV positive patient died of pneumococcal disease. Rather than wait for such an occurrence in the present climate where standards of care prevail, the recommendation should perhaps be either withdrawn or modified to state clearly that clinical efficacy has not been proved in this group of patients. In the meantime, while the present recommendations are in force, clinicians are in a dilemma.

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Surgical bleeding and calcium antagonists

Incidence of bleeding may be lower than suggested

EDITOR,—In L E Wagenknecht and colleagues' prospective randomised placebo controlled study of nimodipine in patients undergoing cardiac valve surgery an interim analysis of 149 patients suggested that nimodipine was associated with bleeding complications leading to increased mortality.[1] In two out of three patients treated with nimodipine who died because of blood loss, however, an underlying haematological disease may have precipitated bleeding, but the authors do not comment on this.

The authors refer to a study in which various calcium antagonists were associated with an increased frequency of haemorrhagic stroke and subdural haematoma among survivors of myocardial infarction, and to a study suggesting increased blood loss from ear incisions in a rabbit model. In both studies, however, recombinant tissue-type plasminogen activator was given in combination with a calcium antagonist.

A haemodynamic and pharmacokinetic study of nimodipine in patients undergoing coronary artery surgery did not show an increased risk of bleeding in this population.[2] A prospecitve randomised placebo controlled study with nimodipine in the prevention and treatment of delayed ischaemia after aneurysmal subarachnoid haemorrhage was conducted in my unit from 1985 to 1988: nimodipine significantly reduced the incidence of delayed ischaemia.[3] In particular, no haemorrhagic complications associated with nimodipine were detected. We have used intravenous nimodipine routinely in subarachnoid haemorrhage since 1988 in over 1500 cases, with no haemorrhagic complications attributed to its use.

As cardiac valve surgery differs considerably from other surgical interventions, especially with respect to pharmacological management, it does not seem appropriate to conclude that similar problems should emerge during other surgical interventions—for example, repair of an intracranial aneurysm. Furthermore, in two trials in patients with head injury, in which nimodipine was given to a total of 581 patients, no bleeding problems became apparent.[4,5]

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1 Wagenknecht LE, Furberg CD, Hammon WJ, Legault C, Troost BT. Surgical bleeding: unexpected effect of a calcium antagonist. *BMJ* 1995;310:776-7. (25 March.)
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Other causes for increased risk of bleeding are possible

EDITOR,—L E Wagenknecht and colleagues report an increased risk of major surgical bleeding associated with treatment with nimodipine in patients undergoing replacement of a cardiac valve.[1] In other situations nimodipine has been used in thousands of patients without any suggestion of bleeding problems. The common indication for this drug is aneurysmal subarachnoid haemorrhage, in which it undoubtedly reduces delayed ischaemia and improves outcome. In a review of this topic, with 4555 patients receiving intravenous nimodipine and 1271 oral treatment (with a much higher dose of 360 mg/day), surgical bleeding was not mentioned as a problem, although many of the patients had surgery for an aneurysm during their treatment.[2] Furthermore, recurrent bleeding from ruptured aneurysms was not prominent: this complication was noted in 12% of 4489 patients receiving nimodipine or other calcium antagonists and 15% of 523 controls.[2] In our experience of giving nimodipine to 140 patients, only one of 34 with recently ruptured unoperated aneurysms had a recurrent haemorrhage.

If nimodipine had an antihaemostatic effect an increase in less severe perioperative haemorrhage would also be expected. Was there a difference in the overall or median blood loss between the two groups as a whole? What other factors, such as the use of heparin, may have played a part?

Several statistical questions arise, particularly when trials are stopped early.[3] How many interim analyses of data were planned, and what consideration was given to the increased risk of false positive results? The cause specific mortality from haemorrhage was not significantly associated with nimodipine (estimated odds ratio 5·2 (95% confidence interval 0·6 to 45·8)), assuming that the haemorrhage contributed significantly to death in those who both had massive haemorrhage and died: what other factors were considered to explain the difference in mortality? Also, the associations between nimodipine and mortality (odds ratio 6·5 (0·8 to 55·7)) and between nimodipine and haemorrhage (4·4 (0·9 to 21·6) do not reach significance when the two patients with pre-existing blood disorders are excluded. Should consideration be given to another, similar trial in which such disorders are excluded?

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Conflict of interest: N Dorsch has received funding from Bayer and other companies involved in the manufacture of cerebral protective drugs, which has enabled him to address international meetings on these topics.

British aneurysm nimodipine trial reported improved clinical outcome with nimodipine

EDITOR,—L E Wagenknecht and colleagues report a randomised placebo controlled trial, in which the calcium antagonist nimodipine was assessed as a possible neuroprotective agent during cardiac surgery.[1] The trial was stopped prematurely after 149 patients had been enrolled because an interim analsis showed an excess mortality with nimodipine (eight deaths versus one). This excess mortality was strongly associated with major surgical bleeding. The authors state that this was an unexpected finding, observed in a post hoc analysis, and requires further exploration.

Relevant additional data are available from the British aneurysm nimodipine trial.[2] In this pragmatic trial 554 patients with suspected aneurysmal subarachnoid haemorrhage were randomly allocated to receive either oral nimodipine 60 mg every four hours for 21 days or matching placebo. A

striking and highly significant improvement in the clinical outcome at three months was observed in the nimodipine limb. Among all 554 patients, 235 of whom underwent operation, a bleeding event led to nimodipine being stopped in only one patient. This patient suffered a colonic bleed of moderate severity, which the investigator reported as possibly being associated with nimodipine. The patient required a blood transfusion but recovered uneventfully.

"Bleeding" events were reported as an adverse event in two further patients, both of whom had received nimodipine. The first patient was reported to have a rash and haematoma on the back, which the investigator stated was almost certainly related to the use of ceftazidine. The second patient was reported as having thrombocytopenia and anaemia. This was observed 15 days after the treatment with nimodipine was completed, and the investigator reported that these adverse events were possibly related to atenolol, which the patient was receiving at the time.

Thus the data from the British aneurysm nimodipine trial give little support to the findings reported by Wagenknecht and colleagues, which are possibly artefacts, reflecting the authors' post hoc analyses.

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Conflict of interest: Gordon Murray gave statistical advice to the British aneurysm nimodipine trial, which was funded by Bayer, but has no other links with the company.

Authors' reply

EDITOR,—Much of the information provided in the responses to our paper seems to be anecdotal. To settle the question of whether calcium antagonists have a prohaemorrhagic effect a systematic collection of data on blood loss is essential, preferably in a randomised trial. This was a strength of our study. Further support for our observation is the more frequent use of the procoagulant aminocaproic acid (Amicar) in the group treated with nimodipine compared with the placebo group (56% *v* 36%, P=0·01).

Surgical bleeding may possibly be caused by an interaction between calcium antagonists and heparin or thrombolytic drugs, or both. The fact that only 13% of patients receiving nimodipine responded with excessive bleeding perhaps suggests that only some patients were susceptible.

A full report of the study and an extensive literature review are being prepared. Pre-existing blood disorders were found in both study groups, as would be expected in a randomised trial. Removing from the analysis the two patients mentioned in our report is a simplistic approach that breaches the integrity of the original randomisation. We still believe that our unexpected finding requires further exploration.

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Faulty blood bags

Reputation of English blood transfusion service has been unjustly damaged

EDITOR,—I wish to comment on recent reports of faults in some of the blood bags used by the English National Blood Authority.[1] Several of the points made have been misleading and may have given rise to inappropriate public and professional concern.

Firstly, international and published experience confirms that minor defects in plastic blood bags occur infrequently but regularly and that virtually all such defects are screened out during routine quality assurance programmes before blood is issued to hospitals from regional blood transfusion centres. Exceedingly rare (certainly with an incidence of less than one in a million blood transfusions), a defect remains undetected and causes bacterial contamination and consequential septicaemia in the recipient.

Secondly, the English National Blood Authority is to be congratulated for having introduced blood bags from a second supplier into England. This much needed break of the longstanding monopoly on the supply of blood bags must already have saved the NHS in England substantial amounts of money and considerably enhanced the security of quality systems. The competition thereby created must be generating savings approaching £1m a year, much of which will be coming from the original monopoly supplier.

Thirdly, the notion that the authority's second supplier of blood bags (Tuta, Australia) provides products of inferior quality is false. The Scottish National Blood Transfusion Service rejected the proposed monopoly by Baxter in 1966 and for almost 30 years has been purchasing blood bags from both Tuta and Baxter. We have used many millions of both blood bags and have no doubt that Tuta produces a high quality product that, in terms of blood safety, competes equally with the product from Baxter. Both manufacturers have had occasional problems with quality but have always responded expeditiously and in close collaboration with their customers. If doubts have arisen then both manufacturers have had no hesitation in replacing (at no cost to the NHS) any suspect batches of blood bags.

Finally, it is unusual, but not unique, for a product to be recalled from hospital blood banks. Of much greater concern, however, is the perception that this event was deliberately seized on to damage further the public image of the blood transfusion service in England; this is regrettable.

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1 Dyer O. Blood authority investigates faulty blood bags. *BMJ* 1995; 311:145. (15 July.)

Faulty bags were withdrawn from routine use

EDITOR,—Owen Dyer's report on the faulty blood bags withdrawn by the National Blood Authority may have misled readers.[1] He quotes our spokeswoman as saying that "only 5000 of the estimated 7000 Tuta bags had been disposed of immediately because some hospitals had no other kind." When the fault in the Tuta bags was first discovered it was thought that the leaking seals had occurred in only a limited number of batches. Initially 5000 bags were withdrawn. The remaining 2000 bags were withdrawn the next week after the manufacturers informed us that the fault was sporadic and not confined to certain batches. The advice issued to hospitals in the Oxford and Southampton areas, some of which had only Tuta bags in stock, was that when no alternative was available their use "must be at individual clinical discretion and the blood pack must be carefully inspected before use." This clearly indicated that the bags should not be issued for routine use but should be used only in emergencies.

Dyer also alludes to the costs of the current structure of the National Blood Authority. Before the authority was established the 14 centres in England were the responsibility of the regional health authorities. Each centre had its own management team and senior medical staff. In addition there was a national directorate, based in Manchester, whose role was to coordinate the activities of the centres. If the proposals for reorganisation are approved the new management structure will consist of only three administration centres with senior management teams. The chief executive posts in other centres will disappear, and the result will be a more streamlined management structure, less bureaucracy, and lower administrative costs.

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Screening for melanoma

EDITOR,—When Duncan Keeley states in his commentary to our paper that "feasibility studies . . . that fail to address these issues [workload, earlier diagnosis, and anxiety] should not be undertaken,"[1] he ignores appropriate study design. Ours was a validation study: validity must be proved before money is spent on feasibility studies. Furthermore, such pragmatic outcomes are not appropriate in validation studies because the intensive assessment may well affect patient behaviour.

Keeley suggests that workload would "substantially increase." However, opportunistic screening when patients attend for other reasons would minimise the workload of mole counts—for example, general practitioners could send instructions for self screening or give a leaflet or perform a mole count, or both, when checking blood pressure. Alternatively, community campaigns could advise self screened people at high risk to avoid being sunburnt. The workload would partly depend on the potential to induce anxiety, and here Keeley also automatically assumes "significant adverse consequences." This ignores evidence that reassuring messages, practical advice to minimise risk, and emphasising benefits can allay fears without stopping a change in behaviour (M Johnston, King's Fund Centre conference, London, November 1994). To assume that outcomes will be poor is unjustified for both anxiety and workload.

Targeting populations who have greater need is apparently "unacceptable," despite improving the efficiency of the intervention. Should community or population approaches never be targeted in higher risk areas, where melanoma is common, either?

Keeley's preferred research areas may suffer the limitations of screening. Population approaches could also increase anxiety and workload, and thus not necessarily be any more cost effective, particularly as a fifth of the population (patients with many moles or freckles) account for most cases. Improving doctors' skills will work only if patients attend with moles that are changing—that is, self assessment or screening would need to be encouraged.

The implication is that screening would have a high ratio of cost to benefit. It takes seconds to count moles (the median count for trunk or arm is 2-3), and with reassurance and advice screening could feasibly take 2-3 minutes. If every patient